Urinary Output of Adrenaline and Noradrenaline in Severe Thermal Burns *

McC. GOODALL,** C. STONE, B. W. HAYNES, JR.
Durham, North Carolina

From the Department of Physiology, Duke University School of Medicine, Durham, North Carolina, and the Department of Surgery, Medical College of Virginia, Richmond, Virginia

INTRODUCTION

THE HUMAN adrenal gland contains 220 to 840 μg. of adrenaline and 44 to 160 μg. of noradrenaline per gram of tissue.[25] Adrenaline is now generally accepted as being the principal hormone of the adrenal medulla,[19, 24, 26, 44, 52] while noradrenaline is the neurohormone of the sympathetic nerves.[2, 5, 13, 19, 21, 23, 24, 33, 35, 45, 48, 64] Both of these hormones are excreted in the urine and the quantity excreted seems to parallel the quantity of these hormones produced by the adrenal gland and the sympathetic nerves.[24] Von Euler [27] showed that normal young adults excreted approximately 11.5 μg. of adrenaline and 29 μg. of noradrenaline per 24 hours. However, the quantity varied during periods of rest and activity, being decreased with rest and elevated with activity.[24, 28]

The urinary output of adrenaline and noradrenaline is increased under various conditions such as muscular exercise,[28] exposure to centrifugation,[46] flying,[32] thyrotoxicosis,[66] subsequent to trauma,[24, 36] and psychomotor disturbances.[9, 37] In pheochromocytoma and sympathetic nerve tumors, the urinary output of either or both of these catechols is markedly elevated.[17, 42, 49] In postural hypotension the urinary output of noradrenaline is decreased, but that of adrenaline is only slightly depressed.[57] Both hypoglycemia [15] and insulin shock [7, 16, 31, 50] increase the excretion of adrenaline.

After unilateral adrenalectomy there is no change in the output of adrenaline or noradrenaline, but after bilateral adrenalectomy, there is approximately an 80 per cent fall in the adrenaline output, and little or no change in the noradrenaline output.[26] This indicates that most of the adrenaline excreted originates from the adrenal gland and that the noradrenaline comes principally from other sources.

Heretofore, the urinary output of adrenaline and/or noradrenaline subsequent to severe thermal burns has not been reported, although a number of investigators [11, 18, 60, 70, 71] have noted indirect evidence of adrenal medullary activity associated with burns, and Evans [18] described a "burn stress pseudo diabetes." In the light of the evidence presented in this paper, the hyperglycemia and glycosuria associated with burns would seem to be clearly related to an increase in adrenal medullary activity with a rise in production of adrenaline. Adrenaline has a marked glycogenolytic effect [51] and hyperglycemic action.[7, 15, 50, 67]

The relationship of the sympathetic neurohormone noradrenaline to burns has been less clear, although an increased output of this hormone has been noted in trauma and infection.[36] Furthermore, a number of investigators have been impressed with the importance of this hormone in shock therapy [1, 14, 19, 41, 53, 59, 74] and its use in the treatment of hypotension associated with surgical conditions.[6, 8, 12, 14, 59, 63, 69]

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** Established Investigator, American Heart Association.

In view of adrenaline's importance in metabolism,[39, 43, 58, 67, 72] vascular [4, 22, 29, 34, 40] and cardiac activity,[3, 10, 39, 43, 61] and in view of noradrenaline's role as the principle physiological agent for maintaining vascular tone,[4, 10, 22, 24, 30, 34, 35, 38, 40, 41, 53, 54, 59, 62, 68, 74] it was felt that the output of these two hormones should be evaluated in burns.

METHOD

The various modifications of the fluorometric and colorimetric methods in present day use for determining adrenaline and noradrenaline are unsatisfactory because urine, plasma and whole blood contain adrenaline and noradrenaline precursors,[55, 56, 73] a number of amino acids, and other constituents, which are fluorometrically and colorimetrically active [22, 24, 65] and therefore impart an error to the determinations. For this reason, the bioassay [20, 27, 44] which gives more accurate and specific results has been used in these experiments.

1. *General.* The 24-hour urines were collected by the Department of Surgery, Medical College of Virginia, from burned patients under their care and forwarded by Air Mail Special Delivery to the Department of Physiology, Duke University, where the urines were biossayed for adrenaline and noradrenaline. The 24-hour urines were collected at first daily and then every third day for four weeks, and thereafter weekly until death or recovery.

2. *Preparation of Urine Extract.* The procedure was adopted from von Euler and Hellner.[27] The urine was hydrolyzed and the adrenaline and noradrenaline selectively adsorbed on aluminum hydroxide and filtered. The precipitate was washed and redissolved with 2N sulphuric acid. The remaining salts were precipitated out by mixing the extract with alcohol and acetone. The filtrate was concentrated in vacuo.

3. *Biological Assay.* a) *Cat's Blood Pressure.* The cat's blood pressure was recorded from the carotid artery and injections of adrenaline, noradrenaline and urinary extract were made into the femoral vein.

b) *Fowl's Rectal Cecum.* Two to three centimeters of the hen's rectal cecum was suspended in Tyrode's solution at 39° C. Through the Tyrode solution, 6.5 per cent CO_2 in oxygen was bubbled. Injections of adrenaline, noradrenaline and urinary extract were made into the bath and the degree of cecal relaxation was recorded.

4. *Computation of Results.* Having determined the activity ratio for adrenaline and noradrenaline on the cat's blood pressure and on the hen's rectal cecum, and the activity of the unknown urinary extract in terms of l-noradrenaline, it is possible to calculate the relative amounts of adrenaline and noradrenaline in the urinary extract. The following symbols are used for such calculation:

a = l-noradrenaline equivalents in μg. per ml. of urine on cat's blood pressure.
A = l-noradrenaline equivalents in μg. per ml. of urine on hen's rectal cecum.
q = Activity ratio l-adrenaline : l-noradrenaline on cat's blood pressure.
Q = Activity ratio l-adrenaline : l-noradrenaline on hen's rectal cecum.

The amount of l-noradrenaline and l-adrenaline may then be calculated as follows:

$$x = \mu g./ml. \text{ of adrenaline or } \frac{A - a}{Q - q}$$

$$y = \mu g./ml. \text{ of l-noradrenaline or } A - xQ$$

RESULTS

The normal urinary levels of adrenaline and noradrenaline were determined from the 24-hour specimens of normal adult males varying in age from 20 to 40 years. Calculated on the basis of 24-hour output, the average quantity of adrenaline excreted was 15.7 μg., and noradrenaline 32.3 μg. These figures compare favorably with the normal output as determined by U. S. von

TABLE I. *Urinary Adrenaline and Noradrenaline of Burned Patients Who Recovered*

Days Post-Burn	Calculated 24-Hour Output of Adrenaline and Noradrenaline							
	T. C., male, 24 yrs., 29% burn		N. B., male, 32 yrs., 39% burn		J. V., male, 35 yrs., 24% burn		L. B., female, 33 yrs., 21% burn	
	Adr.	Nor.	Adr.	Nor.	Adr.	Nor.	Adr.	Nor.
Control	15.7	32.3	15.7	32.3	15.7	32.3	15.7	32.3
1	40.6	191.9	89.7	118.6	109.4	316.9	32.4	151.2
2			44.6	181.4			36.6	140.3
3	46.6	216.5			14.6	97.0	36.6	225.7
4			28.8	152.4	32.7	102.5	39.1	179.3
5	91.2	176.0	23.3	135.8				
6			32.9	75.4	29.0	123.4	23.0	180.8
7	54.7	269.0	30.9	91.0	14.6	203.1		
8							25.4	163.6
9			29.5	117.9				
10	41.8	187.9					51.2	64.1
11	51.8	155.5	37.9	131.6				
12					46.7	121.2	34.5	61.0
13			55.0	117.9				
14							22.8	71.5
15			62.6	134.1	51.2	166.7		
16	58.2	182.0					37.3	53.6
17			148.0	122.1				
19	10.8	108.4			27.2	198.7		
20			58.5	188.1	18.0	127.9		
21							22.7	51.5
23	14.4	105.1	55.3	147.4	24.8	115.3		
24							27.5	55.1
25	21.6	131.8						
27			69.9	237.1	21.6	51.0	11.9	71.4
28	55.0	160.3			23.5	141.0		
5 wks.	30.2	201.0	33.3	171.4	26.6	152.0	20.2	69.1
6 wks.	59.9	195.4	33.0	184.5	24.8	131.4	13.3	156.4
7 wks.	65.5	277.2	82.4	485.5	53.4	87.3	15.2	76.6
8 wks.			15.0	245.0	23.1	170.0		
9 wks.			40.1	188.8	19.8	100.3		
10 wks.			4.9	110.3	20.5	155.3		
11 wks.	26.7	235.5	47.7	97.9	17.5	190.1	*16.1	99.3
12 wks.	38.4	123.6	28.7	143.5	22.5	202.5		
13 wks.	38.8	135.8	18.9	60.2	11.4	171.6		
14 wks.	47.8	136.2	4.1	20.7	*29.9	128.3		
15 wks.	69.8	178.3	17.7	106.2				
17 wks.	64.8	108.0	5.8	38.6				
18 wks.	41.9	100.1	6.7	44.8				
19 wks.	57.8	117.7	*6.7	58.8				
20 wks.	56.7	129.6						
21 wks.	38.2	95.6						
25 wks.	28.3	75.1						
35 wks.	*17.2	42.0						

* Discharged from hospital.

Euler.[27] Values much in excess of these figures are generally the result of some underlying adrenal sympathetic stimulation.

Urines from 14 burned patients were assayed for adrenaline and noradrenaline. Patients varied in age and degree of burn. As seen from the urinary determinations of adrenaline and noradrenaline, subjects could be divided into three well defined categories: 1) those who recovered with

TABLE II. *Urinary Adrenaline and Noradrenaline of Burned Patients Who Died with High Adrenaline and Noradrenaline Output*

Days Post-Burn	Calculated 24-Hour Output of Adrenaline and Noradrenaline							
	J. A., female, 66 yrs., 25% burn		J. H., female, 12 yrs., 88% burn		R. C., male, 65 yrs., 38½% burn		N. J., female, 44 yrs., 22% burn	
	Adr.	Nor.	Adr.	Nor.	Adr.	Nor.	Adr.	Nor.
Control	15.7	32.3	15.7	32.3	15.7	32.3	15.7	32.3
1	86.5	283.9			50.9	187.2	214.2	462.3
2	126.9	324.0					184.9	303.9
3			Delay in		48.3	165.6	214.2	512.5
4	105.9	308.9	entering		111.5	78.1	*243.5	570.5
6	Destroyed		Hospital		140.3	161.5		
7	in transit				30.2	226.5		
8	112.3	425.1						
10	99.8	307.7	91.0	119.9	25.6	161.4		
11			112.0	113.8				
12	117.7	299.6	184.6	139.1	70.1	287.2		
13			183.1	141.3	*87.8	280.8		
14	69.5	384.3	93.6	138.8				
16			152.5	199.3				
17	79.8	336.0						
18			*224.3	253.7				
21	196.6	334.8						
23	116.4	397.2						
26	*261.4	389.1						

* Died.

gradual return of the urinary adrenaline and noradrenaline to normal levels, see Table I; 2) those who died with an elevated adrenaline and noradrenaline output, see Table II; and 3) those who died with low output levels of adrenaline and an elevated output of noradrenaline, see Table III.

In group I (see Table I), patients subsequent to burn showed an immediate rise in the urinary output of adrenaline and noradrenaline. The elevated catechol amine excretion remained high for a period of two weeks to three months, depending largely upon the extent of burn and recovery of the patient. The excretion rate of these hormones gradually returned to normal. Temporary exacerbations were noted after skin grafts, emotional upsets, intercurrent infection, etc. On occasions the 24-hour adrenaline output exceeded 100 μg. and the noradrenaline exceeded 250 μg. per 24 hours (see patient T. C., Table I). This, however, was not the rule, for prior to recovery the adrenaline most often remained in the range of 35 μg. to 75 μg. per 24 hours, and the noradrenaline 100 μg. to 200 μg. per 24 hours, a level which was three to seven times above control values.

In group II (see Table II), patients also showed subsequent to burn an immediate rise in the output of adrenaline and noradrenaline. In this group of patients the adrenaline-noradrenaline urinary output reached very high levels and remained elevated until death. Daily urinary adrenaline output ranged from 25 μg. to 260 μg. per 24 hours and noradrenaline output from 78 μg. to 570 μg. per 24 hours. This represented levels two to 26 times above normal. There appeared an additional rise in the output of these hormones on the day preceding, and the day of death.

Group III (see Table III) was composed of patients who also showed subsequent to burn a marked rise in the urinary

TABLE III. *Urinary Adrenaline and Noradrenaline of Burned Patients Who Died with Low Adrenaline Output*

Days Post-Burn	Calculated 24-Hour Output of Adrenaline and Noradrenaline					
	N. W., male, 54 yrs., 37% burn		J. J., male, 44 yrs., 50% burn		I. T., male, 32 yrs., 31% burn	
	Adr.	Nor.	Adr.	Nor.	Adr.	Nor.
Control	15.7	32.3	15.7	32.3	15.7	32.3
1	58.5	235.3	118.3	111.5	287.3	171.0
2	Destroyed in transit		82.8	176.2	84.9	209.9
3	31.2	111.6	42.8	183.0	29.5	373.2
4	19.2	160.0	19.6	98.0	101.4	541.8
5	11.4	184.2	16.6	83.0	*23.9	143.6
6			44.1	160.0		
7	14.3	187.3	*33.4	104.4		
9	*30.8	386.5				
	B. B., female, 30 yrs., 45% burn		E. B., female, 47 yrs., 55% burn		M. H., male, 68 yrs., 33% burn	
	Adr.	Nor.	Adr.	Nor.	Adr.	Nor.
Control	15.7	32.3	15.7	32.3	15.7	32.3
1	105.0	176.4	48.9	71.4	50.5	166.3
2	Destroyed in transit		11.9	74.2	*43.7	343.2
3			8.4	66.3		
4	31.5	138.5	*3.7	47.6		
5	11.0	90.8				
6	69.9	221.3				
7	*32.7	131.6				

* Died.

output of noradrenaline. The adrenaline output, however, was only slightly elevated the first post-burn days, and thereafter declined. In this group of patients the noradrenaline output ranged from approximately 50 μg. to approximately 550 μg. per 24 hours and remained elevated until death. The adrenaline output on the other hand was only moderately elevated the first post-burn days and then gradually returned to normal or sub-normal levels. The adrenaline output in some patients of this group was slightly elevated on the terminal date. In no case did the adrenaline output seem commensurate with the high degree of "stress" imposed by the burn itself.

DISCUSSION

From the results described it seems that the urinary adrenaline-noradrenaline output roughly parallels the degree of burn, for the greater the degree of burn, the greater the output of these two hormones (Table I and Table II). This would appear to follow the usual pattern of adrenaline-noradrenaline output subsequent to muscular exercise [28] and trauma.[36]

It is known that adrenaline originates principally from the adrenal medulla,[19, 24, 26, 44, 52] and noradrenaline from the sympathetic nerves.[2, 5, 13, 19, 21, 23, 24, 33, 35, 45, 48, 64] It is not clear why the output of these two hormones is elevated in burns. It would seem that since adrenaline is of fundamental importance in general metabolism,[39, 43, 58, 67, 72] vascular [4, 22, 29, 34, 40] and cardiac activity,[3, 10, 39, 43, 61] its increased release and output is of key importance in burns and the recovery from them. This appears even more logical, since in burned patients the increased output of adrenaline is prolonged for weeks and even months after the burn,

and does not return to normal levels until total recovery. Since the increased output of adrenaline continues long after the initial stress of the burn, this would lead one to believe that adrenaline is important to the reparation metabolic processes associated with recovery.

Since noradrenaline is a potent physiologic vasoconstrictor [4, 10, 22, 24, 30, 34, 35, 38, 40, 41, 53, 54, 59, 62, 68, 74] and its metabolic effects [58, 67, 72] are secondary to those of adrenaline, it would seem that the initial output of this hormone was associated with the maintenance of vascular tone and the prevention of plasma extravasation. The noradrenaline output gradually decreases as recovery takes place. This would indicate that the output of this hormone is closely related to the physiologic demand, and, that as recovery takes place, the demand decreases.

Group III (see Table III) is unique in that these patients initially showed a rise in adrenaline and noradrenaline output, but thereafter showed a decline in the adrenaline production; the noradrenaline output remained at a high level. Since adrenaline is the chief product of the adrenal medulla,[19, 24, 26, 44, 52] and since its output can be reduced to a very low level by a bilateral adrenalectomy,[26] this would seem to indicate that in this group of patients the deficit in adrenaline output was related directly to the adrenal medulla and its capacity to produce adrenaline. One might then conclude that this group of patients represented a condition resembling an acute adrenal medullary insufficiency. This appears even more plausible in view of recent preliminary evidence [47] which seems to indicate that in burned patients who die showing a sub-normal adrenaline output, the adrenal gland per se has very little adrenaline. Whether this seeming adrenal medullary insufficiency is the cause of death, cannot be ascertained from these results. However, in view of adrenaline's important physiologic action, and, since patients who recovered invariably showed an increased adrenaline output, it certainly seems reasonable to assume that an adequate supply of adrenaline is of importance in the recovery of burned patients. This does not imply that adrenaline or its precursors should be given to burned patients, but it would seem that in selected cases adrenaline and more especially its biologically inactive precursors [55, 56, 73] might prove a helpful adjuvant in the treatment of burns.

SUMMARY

1. Urine from 14 selected burned patients was assayed for adrenaline and noradrenaline. Determinations were made daily and, as recovery took place, every third day, and then weekly.

2. As determined from adult males the normal 24-hour output of adrenaline averaged 15.7 μg. and noradrenaline 32.3 μg.

3. All burned patients, excepting those described in paragraph five below, showed a marked elevation of adrenaline and noradrenaline output. The degree of elevation roughly paralleled the severity of burn. In severely burned patients the daily urinary adrenaline output ranged from 25 μg. to 260 μg. per 24 hours and the noradrenaline from 78 μg. to 570 μg. per 24 hours. The average post-burn urines showed adrenaline and noradrenaline levels eight to 12 times above normal.

4. As recovery took place, there was a gradual return of adrenaline and noradrenaline output to within normal limits.

5. In one group of burned patients, all of whom died, there was a marked initial rise in the noradrenaline output, but only a moderate elevation in the adrenaline output. Whereas the noradrenaline output remained elevated in this group of patients, the adrenaline output gradually fell off to levels sub-normal for the degree of "stress" imposed by the burn. This low adrenaline output seemed to represent a condition commensurate with an acute adrenal medullary insufficiency.

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